Primary Non-Hodgkin's Lymphoma of the Nasal Cavity

Prognostic Significance of Paranasal Extension and the Role of Radiotherapy and Chemotherapy

Ye-Xiong Li, M.D.[1]
Philippe A. Coucke, M.D.[2]
Jian-Ying Li, M.D.[1]
Da-Zhong Gu, M.D.[1]
Xin-Fan Liu, M.D.[1]
Li-Qiang Zhou, M.D.[3]
René-Olivier Mirimanoff, M.D.[2]
Zi-Hao Yu, M.D.[1]
Yi-Rong Huang, M.D.[1]

[1] Department of Radiation Oncology, Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, People's Republic of China.

[2] Department of Radiation Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.

[3] Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, People's Republic of China.

The authors thank Dr. Zheng Rong for her continuous support and critical comments.

Address for reprints: Ye-Xiong Li, M.D., Department of Clinical Investigation, Box 71, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030.

Received October 14, 1997; revision received January 20, 1998; accepted January 20, 1998.

BACKGROUND. This study was conducted to determine whether the paranasal extension of a primary non-Hodgkin's lymphoma (NHL) of the nasal cavity has any deleterious effect on patient outcome.

METHODS. One hundred and seventy-five patients with previously untreated nasal NHL were reviewed. There were 2 with low grade, 107 with intermediate grade, 17 with high grade, and 49 with unclassifiable lymphomas. In 48 cases the immunophenotype was available and 46 were T-cell lymphoma. According to the Ann Arbor system, there were 133 patients with Stage IE, 28 with Stage IIE, 4 with Stage IIIE, and 10 with Stage IVE lymphomas. Stage IE was subdivided into limited Stage IE (i.e., confined to the nasal cavity [67 patients]) or extensive Stage IE (i.e., presenting with extension beyond the nasal cavity [66 patients]). For patients with limited Stage IE disease the treatment of choice was radiotherapy with or without chemotherapy. In patients with extensive Stage IE disease, treatment was comprised of a combination of chemotherapy and radiotherapy or radiotherapy alone. For patients with a more advanced stage of disease (IIE–IVE), chemotherapy was an integral part of the treatment and was completed by irradiation, especially for patients with Stage IIE disease.

RESULTS. The actuarial overall survival (OS) and disease free survival (DFS) rates at 5 years for the whole group were 65% and 57%, respectively. The 5-year OS and DFS rates were influenced by stage, with a gradual decrease from 75% and 68% for Stage IE disease to 35% and 28% for Stage IIE disease, and 31% and 19% for Stage IIIE/IVE disease. Patients with limited Stage IE disease survived significantly longer (90% 5-year OS) compared with those with extensive Stage IE disease (57% 5-year OS; $P < 0.001$). For 67 patients with limited Stage IE disease, the 5-year OS was 89% with radiotherapy alone and 92% with radiotherapy and chemotherapy, whereas for 66 patients with extensive Stage IE disease, the 5-year OS was 54% with radiotherapy and 58% with combined modality therapy or chemotherapy ($P > 0.05$).

CONCLUSIONS. The prognosis of patients with primary NHL of the nasal cavity is stage dependent. In this large cohort of Stage IE patients, it was demonstrated that the paranasal local extension was a significant prognostic factor associated with poorer treatment outcome. The authors believe that Ann Arbor Stage IE should be subclassified further into limited and extensive Stage IE. The addition of chemotherapy did not appear to modify significantly the survival of patients with either limited or extensive Stage IE disease. The extranodal progression observed in patients with extensive Stage IE and Stage IIE-IVE disease clearly illustrates the need for improvement of systemic treatment. ***Cancer*** **1998;83:449–56.**
© 1998 American Cancer Society.

KEYWORDS: non-Hodgkin's lymphoma, nasal cavity, radiotherapy, chemotherapy.

TABLE 1
Treatment Options According to Stage

	Stage				
	Limited IE	Extensive IE	IIE	IIIE/IVE	Total
RT	39	19	5	2	65
RT + Chemo	28	45	22	8	103
Chemo	0	2	1	4	7

RT: radiotherapy; Chemo: chemotherapy.

Primary non-Hodgkin's lymphoma (NHL) of the nasal cavity is a distinct clinicopathologic entity. As an extranodal form of NHL, this disease is characterized by a predominance of T-cell phenotype, a frequent association with Epstein-Barr virus (EBV) infection, and a poor prognosis.[1–12] This particular form of extranodal NHL appears to be relatively more resistant to chemotherapy compared with other forms of NHL.[1,13] In contrast to lymph node NHL, no guidelines for treatment are established for NHL of the nasal cavity.[2,5,14–16] The majority of published series regarding the prognostic factors of NHL of the nasal cavity do not address the effect of paranasal extension, and there was little information regarding the correlation between paranasal extension and prognosis.[1,4,5,8,14,15] The purpose of this investigation was to examine the significance of paranasal extension as a prognostic factor. Therefore, we reviewed what is, to our knowledge, one of the largest series in the world literature of patients treated at the Cancer Hospital of the Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC).

PATIENTS AND METHODS

From January 1983 to December 1995, 195 patients with primary NHL of the nasal cavity were referred to the Cancer Hospital of the CAMS and PUMC in Beijing, China. These patients represent 10% of all patients with NHL at our institution. Patients were deemed eligible provided they were not treated previously elsewhere. After review of pathologic slides, 175 previously untreated patients were considered for the current analysis.

Stage

The patients were staged according to the Ann Arbor system.[17] To assess the prognostic value of paranasal extension, we subclassified Ann Arbor Stage IE into limited and extensive Stage IE. Limited Stage IE tumors were confined to the nasal cavity, whereas extensive Stage IE tumors extended beyond the nasal cavity and into the neighboring structures without any sign of dissemination. For an adequate evaluation the patients underwent a medical history, physical examination, blood chemistry, chest radiograph, and bone marrow aspiration. Computed tomography (CT) and/or ultrasound of the abdomen were performed routinely. In addition, standard radiographs of the bone skull and sinus tomograms as well as CT scans of the head and neck were used systematically to assess the paranasal extension. Chest CT was not routine, but it was performed in 42 patients.

Management

Treatment options were dependent on the stage (Table 1). Limited Stage IE disease primarily was treated by external irradiation with or without consolidation chemotherapy. For extensive Stage IE disease, combined treatment including chemotherapy and radiotherapy was preferred although some of these patients were submitted to radiotherapy alone or chemotherapy alone. In more advanced stage disease a combination of chemotherapy and radiotherapy (Stage IIE) or first-line chemotherapy with adjuvant radiotherapy (Stage IIIE and IVE) generally was used.

Radiotherapy initially was given with an 8-megavolt linear accelerator. The majority of the patients received a dose of 50–55 gray (Gy) with a range of 40–70 Gy. In case of Stage IE disease limited to the nasal cavity, a single anterior port including the nasal cavity and the ipsilateral maxillary/ethmoid sinuses was used in 37 patients. For the remaining 30 patients with limited Stage IE disease, 2 lateral opposing fields and an anteroposterior port were used. The latter technique also was applied to the patients with extensive Stage IE disease. For these particular patients as well as for those with Stage IIE disease, the fields were extended to encompass involved paranasal tissues or cervical lymph nodes. Moreover, 27 of 133 Stage IE patients received prophylactic cervical lymph node irradiation.

Of 175 patients, 103 received chemotherapy in combination with radiotherapy and 7 patients received chemotherapy alone. Fifty-six patients were

treated with a combination of bleomycin, 5 mg/m^2 intravenously (i.v.), on Days 15 and 21; doxorubicin, 25 mg/m^2 i.v., on Days 1 and 8; cyclophosphamide, 650 mg/m^2 i.v., on Days 1 and 8; vincristine, 1.4 mg/m^2 i.v., on Days 1 and 8; and prednisone, 60 mg/m^2 orally on Days 15–28 (BACOP). Twenty-eight patients received bleomycin, 5 mg/m^2 i.v., on Days 15 and 21; etoposide, 60 mg/m^2 i.v., on Days 1–5; cyclophosphamide, 650 mg/m^2 i.v., on Days 1 and 8; vincristine, 1.4 mg/m^2 i.v., on Days 1 and 8; and prednisone, 60 mg/m^2 orally on Days 15–28 (BECOP). Sixteen patients received cyclophosphamide, 750 mg/m^2 i.v., on Day 1; doxorubicin, 50 mg/m^2 i.v., on Day 1; vincristine, 1.4 mg/m^2 i.v., on Day 1; and prednisone, 100 mg orally on Days 1–5 (CHOP). Ten patients received less intensive regimens because of poor performance status, advanced age, or compromised cardiopulmonary function: cyclophosphamide, 750 mg/m^2 i.v., on Days 1 and 8; vincristine, 1.4 mg/m^2 i.v., on Days 1 and 8; bleomycin, 5 mg/m^2 i.v., on Days 1 and 8; and prednisone, 40 mg/m^2 orally on Days 1–10 (COBP) in 2 patients and cyclophosphamide, 650 mg/m^2 i.v., on Days 1 and 8; vincristine, 1.4 mg/m^2 i.v., on Days 1 and 8; procarbazine, 100 mg/m^2 orally on Days 1–14; and prednisone, 40 mg/m^2 orally on Days 1–14 (COPP) in 8 patients. Usually six cycles of combination chemotherapy were administered in cases of advanced stage disease. In contrast, patients with limited Stage IE disease received two to four cycles of consolidation chemotherapy after radiotherapy.

Statistics

The median follow-up time was 70 months. Overall survival (OS) and disease free survival (DFS) were estimated by the product-limit Kaplan-Meier method.[18] Time was measured from the start of initial treatment until the time of first local or distant failure or recurrence, last follow-up, or death. The significance of differences between survival curves was calculated by the log rank test.[19] Multivariate analysis was performed using the Cox model. Comparison of the qualitative data was performed by chi-square analysis.

RESULTS

Patient Characteristics

There were 115 males and 60 females, with a male-to-female ratio of 2:1. The median age was 44 years (range, 11–79 years). The right nasal cavity was involved in 46 patients, the left in 70 patients, and both in 59 patients (Table 2). The most frequent presenting symptom was nasal obstruction. Locally advanced NHL was more likely to be associated with aggressive signs and symptoms including facial swelling, epistaxis, proptosis, hard palate perforation, B symptoms, and cranial nerve palsy.

TABLE 2
Clinical Characteristics of 175 Patients with Nasal NHL

Characteristic	No
Gender	
Male	115
Female	60
Age (yrs)	
Median	44
Range	11–79
Ann Arbor Stage	
IE	133
IIE	28
IIIE	4
IVE	10
B symptoms	58
Paranasal extension by primary tumor	
Maxillary sinus	74
Ethmoid sinus	63
Nasopharynx	43
Nasal skin	22
Hard palate	18
Soft palate	11
Orbit	14
Oropharynx	12
Base of skull	3
Frontal sinus	2
Sphenoidal sinus	2
Immunophenotype	
T-cell	46
B-cell	1
Uncertain	1
Histologic subtypes according to Working Formulation	
Small lymphocytic	2
Diffuse small cleaved cell	18
Diffuse mixed cell	60
Diffuse large cell	29
Immunoblastic	13
Lymphoblastic	4
Unclassifiable	49

NHL: non-Hodgkin's lymphoma.

Paranasal extension was present in 105 patients (60%). Of these, 66 patients (38%) had paranasal extension only, without any sign of lymph node or distant dissemination, and 39 patients (22%) had involvement of lymph nodes or distant extranodal sites as well. The large majority (39 of 42; 93%) of patients with Stage IIE, IIIE, and IVE disease had paranasal extension, and only 3 patients (3 of 42; 7%) had their primary tumor limited to the nasal cavity. The organs or

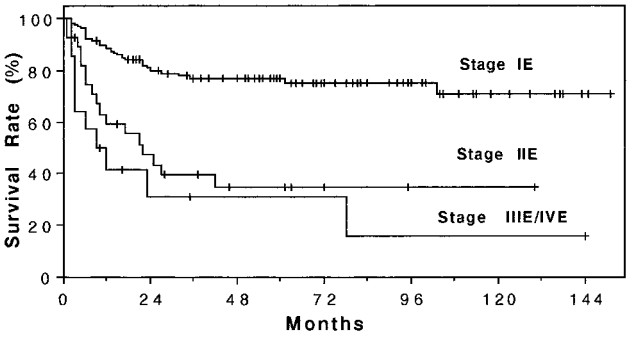

FIGURE 1. Overall survival according to Ann Arbor stage in patients with non-Hodgkin's lymphoma of the nasal cavity for Stage IE (n = 133), Stage IIE (n = 28), and Stage IIIE/IVE (n = 14) patients.

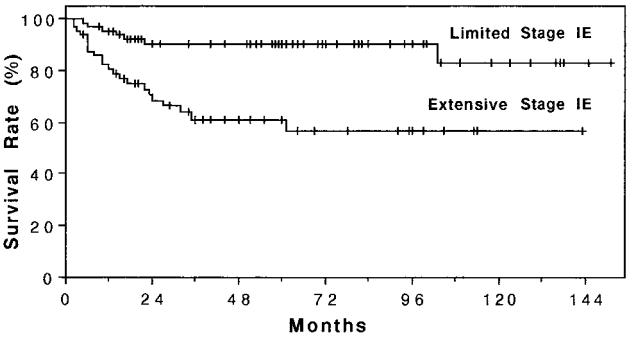

FIGURE 2. Overall survival in patients with limited Stage IE (n = 67) and extensive stage IE (n = 66) disease.

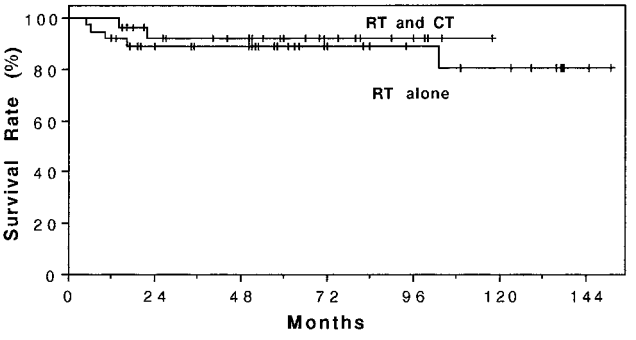

FIGURE 3. Overall survival by treatment in patients with limited Stage IE disease. RT: radiotherapy; CT: chemotherapy.

tissues most frequently involved by the primary tumor were the maxillary sinus (70%), the ethmoid sinus (60%), and the nasopharynx (41%). Approximately 42% of patients (73 of 175) had involvement of multiple neighboring organs or tissues within the vicinity of the primary tumor.

Overall, 21% of the patients (36 of 175) initially presented with lymph node involvement, and 4 of these patients had distant extranodal spread as well. In 20 of these patients the submandibular lymph node was involved, whereas 17 patients presented with positive cervical lymph nodes. Lymph nodes located in the buccal area and in the parotid region were involved less frequently, in three and one patients, respectively. The distant extranodal sites of involvement were observed in the skin, lung, liver, bone marrow, and testis.

Survival

The 5-year OS and DFS were 65% and 57%, respectively. According to the Ann Arbor classification, 5-year OS and DFS were 75% and 68%, respectively, for Stage IE disease, 35% and 28%, respectively, for Stage IIE disease, and 31% and 19%, respectively, for Stage IIIE/IVE disease (Fig. 1). The difference in OS and DFS between Stage IE and IIE disease was statistically significant ($P < 0.001$). However, there was no significant difference in OS and DFS between Stage IIE and Stage IIIE/IVE disease ($P = 0.08$). This partly is due to the small numbers of patients in these subgroups.

The paranasal extension was a significant prognostic factor in Stage IE patients. The 5-year OS and DFS were 90% and 89%, respectively, for limited Stage IE disease, and 57% and 45%, respectively, for extensive Stage IE disease ($P < 0.001$) (Fig. 2). There also was a significant difference in survival between extensive Stage IE and Stage IIE disease ($P < 0.05$).

Chemotherapy, whether combined with radiotherapy or alone, resulted in a 5-year OS of 59%. In contrast, patients treated with radiotherapy alone had a survival probability of 74%, but this merely illustrates a difference in treatment prescription according to stage. Considering 133 Stage IE patients only, the 5-year OS difference was smaller between treatment modalities, with an OS of 79% for radiotherapy alone and 75% for the combined modality therapy or chemotherapy alone. The breakdown in Stage IE patients according to tumor extension and treatment modality shows that for 67 patients with limited Stage IE disease the 5-year OS with radiotherapy alone was 89% compared with 92% for radiotherapy and chemotherapy (Fig. 3). The corresponding survival for 66 patients with extensive Stage IE disease was 54% for radiotherapy alone compared with 58% for chemotherapy or in combination with radiotherapy (Fig. 4). None of these differences were statistically significant. However, it might be worthwhile to note that there was a trend toward better 5-year survival in the group of patients treated with chemotherapy, suggesting that combined modality should be favored in patients

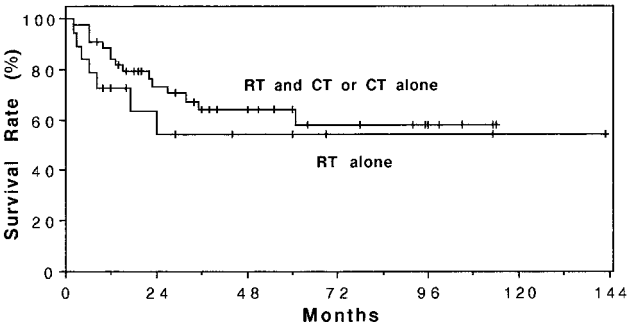

FIGURE 4. Overall survival by treatment in patients with extensive Stage IE disease. RT: radiotherapy; CT: chemotherapy.

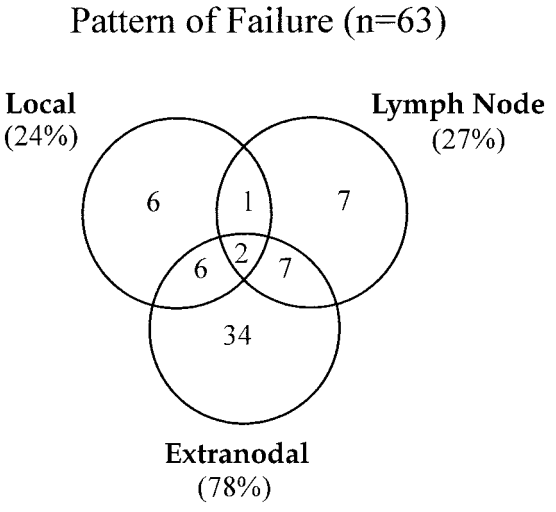

FIGURE 5. Patterns of failure (progression and recurrence) in patients with non-Hodgkin's lymphoma of the nasal cavity.

with extensive Stage IE disease. A comparable analysis could not be performed for higher stage disease.

To assess the influence of prognostic factors on OS and DFS, the following parameters were included in the Cox regression analysis: age, gender, localization, B symptoms, paranasal extension, Ann Arbor stage, pathology, and chemotherapy. Only stage and paranasal extension were significant prognostic factors for OS and DFS.

Patterns of Failure

Forty patients progressed during the initial therapy, and 31 recurred between 2 and 78 months after treatment. The majority of patients (22 of 31; 71%) recurred within 2 years, and 3 recurred at $>$ 5 years. Figure 5 shows the patterns of progression and recurrence in 63 available patients.

For the 15 patients with local progression or recurrence, failure was located in the irradiated field in 11 whereas in 4 patients it was a marginal failure. Only 2 of 67 patients (3%) with limited Stage IE disease developed local recurrence, whereas 9 patients with extensive Stage IE disease local progression or recurrence.

Regional or distant lymph node failure was observed in 17 patients; in 4 of these patients these failures were located in the head and neck region. Prophylactic neck irradiation (PNI) was not used in 106 of 133 Stage IE patients, 2 of whom developed progression in the cervical lymph nodes, whereas none of the remaining 27 Stage IE patients treated with PNI developed cervical progression or recurrence. Systemic lymph node invasion was observed in the axillary, inguinal, abdominal, pelvic, and supratrochlear areas.

Distant extranodal dissemination was the primary patterns of failure. Forty-nine patients (49 of 63; 78%) developed a progression or recurrence in the extranodal sites including the skin, lung, liver, larynx, bone marrow, brain, bone, and testis. Extranodal failure was observed mainly in the skin (24 of 49 patients; 49%), lung (8 patients), and liver (6 patients).

Fifty-six patients died of lymphoma. The origin of death was progression in 35 patients and recurrence in 21 patients. Seven patients died of other causes: cerebral hemorrhage, cerebral thrombosis, myocardial infarction, malignant reticulocytosis, hepatitis, cerebral meningitis, and unknown cause.

DISCUSSION

Primary NHL of the nasal cavity is common in China,[1] accounting for 10% of all NHL in the current study. In contrast, it is rare in the U. S.[5,20] As is the case with nasopharyngeal carcinoma or lymphoma, the higher incidence of nasal NHL in Asian individuals, might be due to the high prevalence of EBV infection.[4,7,10,12,21–24] As observed by other researchers, the most common types are diffuse mixed and large cell lymphomas.[1,5,10] In contrast to primary lymphoma of Waldeyer's ring, which predominantly is of B-cell type,[25] NHL of the nasal cavity mainly is a T-cell lymphoma.[8,9,14,26] With regard to pathology, nasal NHL is characterized by angioinvasion and necrosis. The extensive necrosis, polymorphic cellular infiltration, and small sizes of the biopsy samples usually make subtyping according to the Working Formulation quite difficult.

Pathways of Tumor Spread

Patients with NHL of the nasal cavity usually present at an early stage. However, these early stage tumors often are a bulky primary tumor, and directly extend into the neighboring organs and tissues. The involvement of the maxillary and ethmoid sinuses is the most

common mode of local extension. Conversely, the probability of lymph node and distant extranodal spread increases with extension of the primary tumors outside the nasal cavity.

The major pathway of lymph node spread for NHL of the nasal cavity is to the submandibular and cervical lymph nodes. This submandibular involvement clearly is in contrast to Waldeyer's ring lymphoma in which the cervical lymph nodes are more often involved.[25,27] Moreover, we observed buccal and parotid lymph node spread, which is an uncommon pathway of involvement in other lymphoma. However, the regional lymph node spread of primary NHL of the nasal cavity appears to be consistent with the primary drainage of the nasal cavity and adjacent structures such as the maxillary and ethmoid sinuses.[28]

The propensity of nasal NHL spread to the skin observed at presentation or during progression and recurrence can be explained by the homing capacity of T-lymphocytes that also explain the pattern of spread of other extranodal lymphoma: Waldeyer's ring lymphomas spread to the gut, whereas lung lymphoma spreads to the gut and salivary gland.[29,30]

Management and Prognosis

The prognosis of nasal NHL has been reported to be poor and in general patients with NHL of the nasal cavity are reported to carry an aggressive lymphoma.[1,8,14,16] This study of 175 patients with NHL of the nasal cavity, which to our knowledge is the largest series in the world literature, shows that the prognosis is not uniformly poor and particularly that a subset of patients with Stage IE disease confined to the nasal cavity survives for long periods. Five-year OS and DFS of 90% and 89%, respectively, were obtained when these patients were treated with radiotherapy alone or radiotherapy followed by 2–4 cycles of consolidation chemotherapy. Progression or recurrence rates were low. Thus patients with nasal NHL with limited Stage IE disease should be considered for treatment with radiotherapy with curative intent. Radiotherapy alone or combined with chemotherapy had a similar impact on OS and DFS.

In comparison with patients with limited Stage IE disease, patients with extensive Stage IE disease have a relatively poor prognosis. Nevertheless, the survival for patients with extensive Stage IE disease was significantly better than that for Stage IIE patients. In this series, 67 of 94 patients with extensive Stage IE and Stage IIE disease were treated with combined modality therapy, whereas 24 received radiotherapy alone and 3 received chemotherapy alone. Furthermore, at least 6 cycles of chemotherapy followed by radiotherapy were given to 25 patients with extensive Stage IE disease and 13 patients with Stage IIE disease. Although no significant difference in survival was observed between radiotherapy and combined modality therapy, there is a suggestion that the latter improves the treatment outcome for patients with extensive Stage IE disease. Therefore it is our current policy to combine both treatment modalities for these patients. It is worthwhile to note that in Western countries, chemotherapy followed by involved field radiotherapy is administered to patients with locally advanced lymphoma.[31,32] Recently, several studies have shown that combined modality therapy is better than chemotherapy alone for early stage intermediate and high grade NHL.[31–33]

For patients with limited Stage IE disease who primarily are treated with radiotherapy, we recommend that the treatment volume include the whole nasal cavity and the ipsilateral maxillary and ethmoid sinuses. When the primary tumors are close to the choanae, the nasopharynx is included. For patients with primary tumor extending beyond the nasal cavity, the treatment field is enlarged to encompass the neighboring structures involved by the tumor. We do not recommend prophylactic neck irradiation for Stage IE patients because of the apparent low risk of progression or relapse in the cervical lymph nodes in our experience.

As observed by others,[1,5] patients with Stage IIE and IIIE/IVE disease have an extremely poor prognosis. We recommend chemotherapy as primary treatment with adjuvant irradiation to the primary tumor for these patients. However, survival after 5 years is a rare event, and the use of chemotherapy does not appear to change the uniformly fatal outcome in Stage IIIE and IVE disease. Therefore, given the fact that these patients in the current series were treated with combination chemotherapy (i.e., doxorubicin or etoposide-based regimens), one might consider resistance to conventional chemotherapy to produce any durable long term remissions in these particular patients. It has been reported that resistance to conventional chemotherapy in NHL of the nasal cavity may be associated with frequent expression of p-glycoprotein.[13] Furthermore, loss of p53 function also has been shown to be related to drug resistance in NHL.[34] Therefore, patients with Stage IIIE and IVE NHL of the nasal cavity are candidates for novel treatment strategies or new agents on a clinical trial. In view of the molecular biologic mechanisms, one might consider the use of chemotherapeutic drugs independent of the multidrug resistance gene-related efflux pump or strategies directed toward p53 alteration.

Primary NHL of the nasal cavity is a distinct clin-

ical entity, characterized by a predominance of male and T-cell phenotype, frequent involvement of the paranasal structures, and a high incidence of extranodal progression and recurrence. The prognosis is dependent on the stage and paranasal extension. Patients with Stage IE disease confined to the nasal cavity have a better survival compared with those with Stage IE disease extending beyond the nasal cavity. Patients with Stage IIE, IIIE, and IVE have a poor prognosis that is not significantly influenced by the use of conventional chemotherapy. To our knowledge, this study demonstrates for the first time that prognosis in patients with Ann Arbor Stage IE disease depends on the presence of paranasal extension. Confined or superficial lesions, as is the case in other extranodal sites such as NHL of the stomach, intestine, and Waldeyer's ring,[15,35–38] are cured readily, but spread beyond the boundaries of the primary organ, often resulting in progressive lymphoma. Therefore, Ann Arbor Stage IE NHL of the nasal cavity is subdivided into limited and extensive Stage IE disease. Extensive paranasal extension can be considered to be an independent prognostic factor in subsequent studies and most likely may be used for stratification of patients.

REFERENCES

1. Liang R, Todd D, Chan TK, Chiu E, Lie A, Kwong YL, et al. Treatment outcome and prognostic factors for primary nasal lymphoma. *J Clin Oncol* 1995;13:666–70.
2. Senan S. The diagnosis and treatment of nasal lymphoma: an important cause of upper respiratory tract destruction. *Clin Otolaryngol* 1992;17:563–6.
3. Yamanaka N, Harabuchi Y, Kataura A. The prognostic value of Ki-67 antigen in non-Hodgkin lymphoma of Waldeyer ring and the nasal cavity. *Cancer* 1992;70:2342–9.
4. Campo E, Cardesa A, Alos L, Palacin A, Cobarro J, Traserra J, et al. Non-Hodgkin's lymphomas of the nasal cavity and paranasal sinuses: an immunohistochemical study. *Am J Clin Pathol* 1991;96:184–90.
5. Abbondanzo SL, Wenig BM. Non-Hodgkin's lymphoma of the sinonasal tract: a clinicopathologic and immunophenotypic study of 120 cases. *Cancer* 1995;75:1281–91.
6. Harabuchi Y, Imai S, Wakashima J, Hirao M, Kataura A, Osato T, et al. Nasal T-cell lymphoma causally associated with Epstein-Barr virus: clinicopatholigic, phenotypic, and genotypic studies. *Cancer* 1996;77:2137–49.
7. Mishima K, Horiuchi K, Kojya S, Takahashi H, Ohsawa M, Aozasa K. Epstein-Barr virus in patients with polymorphic reticulosis (lethal midline granuloma) from China and Japan. *Cancer* 1994;73:3041–6.
8. Ferry JA, Sklar J, Zukerberg LR, Harris NL. Nasal lymphoma: a clinicopathologic study with immunophenotypic and genotypic analysis. *Am J Surg Pathol* 1991;15:268–79.
9. Chan JKC, Ng CS, Lau WH, Lo STH. Most nasal/nasopharyngeal lymphomas are peripheral T-cell neoplasms. *Am J Surg Pathol* 1987;11:418–29.
10. Ye YL, Zhou MH, Lu XY, Dai YR, Wu WX. Nasopharyngeal and nasal malignant lymphoma: a clinicopathological study of 54 cases. *Histopathology* 1992;20:511–6.
11. Arber DA, Weiss LM, Albujar PF, Chen YY, Jaffe ES. Nasal lymphomas in Peru. High incidence of T-cell immunophenotype and Epstein-Barr virus infection. *Am J Surg Pathol* 1993;17:392–9.
12. Kanavaros P, Lescs MC, Briere J, Divine M, Galateau F, Joab I, et al. Nasal T-cell lymphoma: a clinicopathologic entity associated with peculiar phenotype and with Epstein-Barr virus. *Blood* 1993;81:2688–95.
13. Yamaguchi M, Kita K, Miwa H, Nishii K, Oka K, Ohno T, et al. Frequent expression of P-glycoprotein/MDR1 by nasal T-cell lymphoma cells. *Cancer* 1995;76:2351–6.
14. Itami J, Itami M, Mikata A, Tamaru JI, Kaneko T, Ogata H, et al. Non-Hodgkin's lymphoma confined to the nasal cavity: its relationship to the polymorphic reticulosis and results of radiation therapy. *Int J Radiat Oncol Biol Phys* 1991;20:797–802.
15. Tran LM, Mark R, Fu YS, Calcaterra T, Juillard G. Primary non-Hodgkin's lymphomas of the paranasal sinuses and nasal cavity: a report of 18 cases with stage IE disease. *Am J Clin Oncol* 1992;15:222–5.
16. Liang R, Todd D, Chan TK, Chiu E, Choy D, Loke SL, et al. Nasal lymphoma: a retrospective analysis of 60 cases. *Cancer* 1990;66:2205–9.
17. Carbone PP, Kaplan HS, Mushoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 1971;31:1860–1.
18. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
19. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part II. Analysis and examples. *Br J Cancer* 1977;35:1–39.
20. Greiner TC, Medeiros LJ, Jaffe ES. Non-Hodgkin's lymphoma. *Cancer* 1995;75:370–80.
21. Kanavaros P, Briere J, Lescs MC, Gaulard P. Epstein-Barr virus in non-Hodgkin's lymphomas of the upper respiratory tract: association with sinonasal localization and expression of NK and/or T-cell antigens by tumour cells. *J Pathol* 1996;178:297–302.
22. Lee JH, Lee SS, Park JH, Kim YW, Yang MH. Prevalence of EBV RNA in sinonasal and Waldeyer's ring lymphomas. *J Korean Med Sci* 1994;9:281–8.
23. Weiss LM, Gaffey MJ, Chen YY, Frierson HF. Frequency of Epstein-Barr viral DNA in "Western" sinonasal and Waldeyer's ring non-Hodgkin's lymphomas. *Am J Surg Pathol* 1992;16:156–62.
24. Van Gorp J, Weiping L, Jacobse K, Liu YH, Li FY, De Weger RA, et al. Epstein-Barr virus in nasal T-cell lymphomas (polymorphic reticulocytosis/midline malignant reticulocytosis) in western China. *J Pathol* 1994;173:81–7.
25. Ko YH, Lee JD, Kim CM, Kim IS, Lee MJ. Malignant lymphomas of the nasal cavity and Waldeyer's ring: clinicopathologic and immunohistochemical study. *J Korean Med Sci* 1992;7:314–24.
26. Emile JF, Boulland ML, Haioun C, Kanavaros P, Petrella T, Delfar-Larue MH, et al. CD5 - CD 56 + T-cell receptor silent peripheral T-cell lymphomas are natural killer cell lymphomas. *Blood* 1996;87:1466–73.
27. Lu YX, Sun WY, Cao J, Shao LH. Clinicopathological and immunohistochemical features of malignant lymphoma of the Waldeyer's ring: a report of 191 cases. *Chin J Oncol* 1991;13:456–8.

28. Gabella G. Cardiovascular system. In: Williams PL, Bannister LH, Berry MM, Collins P, Dyscon M, Dussek JE, et al., editors. Gray's anatomy. 38th edition. New York: Churchill Livingstone, 1995:1451–626.
29. Aisenberg AC. Coherent view of non-Hodgkin's lymphoma. *J Clin Oncol* 1995;13:2656–75.
30. Picker LJ, Butcher EC. Physiological and molecular mechanisms of lymphocyte homing. *Annu Rev Immunol* 1992;10: 561–91.
31. Logsdon MD, Ha CS, Kavadi VS, Cabanilas F, Hess MA, Cox JD. Lymphoma of the nasal cavity and paranasal sinuses: improved outcome and altered prognostic factors with combined modality therapy. *Cancer* 1997;80:477–88.
32. Miller T, Dahlberg S, Cassady J, Spier C, Grogan T, Carlin S, et al. Three cycles of CHOP (3) plus radiotherapy (RT) is superior to eight cycles of CHOP (8) alone for localized intermediate and high grade non-Hodgkin's lymphoma (NHL): a Southwest Oncology Group Study. In:Perry MC, editor. Proceedings of the Thirty-Second Annual Meeting of the American Society of Clinical Oncology, Philadelphia, Pennsylvania, May 18–21, 1996.
33. Glick J, Kim K, Earle J, O'Connell M. An ECOG randomized phase III trial of CHOP vs. CHOP + radiotherapy (XRT) for intermediate grade early stage non-Hodgkin's lymphoma (NHL). In: Perry MC, editor. Proceedings of the Thirty-First Annual Meeting of the American Society of Clinical Oncology, Los Angeles, California, May 20–23, 1995.
34. Wilson WH, Teruya-Feldstein J, Fest T, Harris C, Steinberg SM, Jaffe ES, et al. Relationship of p53, bcl-2, and tumor proliferation to clinical drug resistance in non-Hodgkin's lymphomas. *Blood* 1997;89:601–9.
35. Krol AD, Hermans J, Kramer MH, Kluin PM, Kluin-Nelemans HC, Blok P, et al. Gastric lymphomas compared with lymph node lymphomas in a population-based registry differ in stage distribution and dissemination patterns but not in patients survival. *Cancer* 1997;79: 390–7.
36. Zucca E, Roggero E. Biology and treatment of MALT lymphoma: the state-of-the-art in 1996: a workshop at the 6th International Conference on Malignant Lymphoma. *Ann Oncol* 1996;7:787–92.
37. Shih LY, Liaw SJ, Kuo TT. Primary small-intestinal lymphomas in Taiwan: immunoproliferative small-intestinal disease and nonimmunoproliferative small-intestinal disease. *J Clin Oncol* 1994;12:1375–82.
38. Nakamura S, Akazawa K, Yao T, Tsuneyoshi M. Primary gastric lymphoma: a clinicopathologic study of 233 cases with special reference to evaluation with the MIB-1 index. *Cancer* 1995;76:1313–24.